54, lines 5-11. Support for new claims 19-24 may be found in the subject specification on page 27, Table 1; page 20, line 33 to page 21, line 27. Support for new claims 19-21 may also be found in U.S. Serial No. 07/182,501 on page 54, lines 5-11. Support for new claim 22 may be found in the subject specification on page 27, Table 1, Example 2 (pages 27-29); and in U.S. Serial No. 07/182,501 on pages 57-58. Support for new claims 23-24 may be found in the subject specification on page 12, lines 1-11. Accordingly, applicants respectfully request entry of this Amendment and claims 13-24 are now pending in the subject application.

**Rejection Under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 16-18 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that the specification lacks complete deposit information for the deposit of the hybridoma cell lines secreting monoclonal antibodies OD3 (HB 10204), NB-3 (HB 10205), and TA-1 (HB 10206). The Examiner stated that while the specification provides enough information for one of skill in the art to produce hybridoma cell lines secreting antibodies with the same or similar properties as monoclonal antibodies OD3, NB-3 and TA-1, reproduction of the identical cell lines and antibodies is an unpredictable event. The Examiner stated that because it does not appear that monoclonal antibodies OD3, NB-3 and TA-1 are known and publicly available or can be reproducibly isolated from nature without undue experimentation, and because claims 16-18 specifically require hybridoma cell lines secreting monoclonal antibodies OD3, NB-3 and TA-1, a suitable deposit of the hybridoma cell lines is required

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for patent purposes.

The Examiner stated that applicant's referral to the deposit of HB 10204, HB 10205 and HB 10206 on page 9 of the specification is insufficient assurance that all of the conditions of 37 CFR §1.801-1.809 have been met.

The Examiner stated that if the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants or assignees, or a statement by an attorney of record over his or her signature and registration number, stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required. The Examiner further stated that this requirement is necessary when a deposit is made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each member State. The Examiner stated that amendment of the specification to recite the date of the deposit and the complete name and address of the depository is required.

In response, applicants traverse the rejection of claims 16-18 under 35 U.S.C. §112, first paragraph. Applicants point out that the specification recites the date of the deposit and the complete name and address of the depository (see page 9, lines 1-18, "Statement of Deposit").

In further response, applicants submit herewith as **Exhibit A** a copy of the Budapest Treaty deposit receipt for hybridoma OD3, deposited under ATCC Accession No. HB 10204, hybridoma NB-3, deposited under

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ATCC Accession No. HB 10205, and hybridoma TA-1, deposited under ATCC Accession No. HB 10206. These hybridomas have been deposited with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland, 10852, pursuant to and in satisfaction of the Budapest Treaty on the International Recognition of Microorganisms for Purposes of Patent Procedure. All restrictions upon the availability to the public of the material deposited under ATCC Accession Nos. 10204, 10205, and 10206 will be irrevocably removed upon the issuance of a patent from the subject application.

Furthermore, the undersigned attorney states that the above referenced deposited strain will be permanently maintained with all the care necessary to keep it viable and uncontaminated in the public depository for a period of thirty (30) years from the date of deposit, or at least five (5) years after the last request for a sample of the deposited material, or for the enforceable life of the patent, whichever is longer.

In view of the above discussion, and the statement in compliance with the requirements of 35 U.S.C. §112, first paragraph, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 16-18 under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure.

**Rejection Under 35 U.S.C. §102(a) - McKenzie et al.**

The Examiner rejected claims 13 and 15-18 under 35 U.S.C. §102(a) as being anticipated by McKenzie et al. (Oncogene, vol. 4, no. 5, pp. 543-548, May 1989).

The Examiner stated that McKenzie et al. disclose hybridoma cell lines secreting OD3 (HB 10204), NB-3 (HB 10205), and TA-1 (HB 10206), all of which bind the extracellular domain of the human neu

gene product. The Examiner further stated that the first parent application of the instant application to disclose this series of hybridomas cell lines and monoclonal antibodies appears to be serial no. 07/412,668, filed on September 29, 1989. The Examiner alleged that the McKenzie et al. reference is prior art because its publication date is earlier than September 1989, and its authorship differs from the instant inventive entity.

In response, applicants respectfully traverse the rejection of claims 13 and 15-18 under 35 U.S.C. §102(a). Applicants contend that the subject matter of the currently pending claims is supported in U.S. Serial No. 07/182,501, filed April 18, 1988. The '501 application is a related parent application of the subject application. Specifically, on page 54 of the '501 application, monoclonal antibodies designated TA1 and OD3 and NB3 are disclosed. In addition, hybridomas which secrete such antibodies are also disclosed on page 54 of the '501 application. Applicants also draw the Examiner's attention to pages 57-58 and original claims 14-16 of the '501 application wherein monoclonal antibodies specific for the extracellular domain of neu encoded gene product are disclosed. Applicants maintain that McKenzie et al. is therefore an improper reference under 35 U.S.C. §102(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Rejection Under 35 U.S.C. §102(a) - Masuko et al.**

The Examiner rejected claims 13 and 15 under 35 U.S.C. §102(a) as being anticipated by Masuko et al. (Jpn. J. Cancer Res., vol. 80, pp. 10-14, January 1989).

The Examiner stated that Masuko et al. disclose a hybridoma cell line secreting a monoclonal antibody (SV2-61) which recognizes the extracellular domain of the human neu gene product (see abstract).

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In response, applicants respectfully traverse the rejection of claims 13 and 15 under 35 U.S.C. §102(a) as being anticipated by Masuko et al. Applicants refer the Examiner to the discussion hereinabove of support for the presently pending claims in U.S. Serial No. 07/182,501, filed April 18, 1988. Applicants maintain that the Masuko et al. reference is not a proper reference under 35 U.S.C. §102(a).

In view of the above remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 15 and 18 under 35 U.S.C. §102(a).

**Rejection Under 35 U.S.C. §102(b) - Drebin et al. in light of Disis et al.**

The Examiner rejected claims 13 and 15 under 35 U.S.C. §102(b) as being anticipated by Drebin et al. (Nature, vol. 312, no. 5994, pp. 545-548, December 1984) in light of Disis et al. (Journal of Immunology, vol. 156, no. 9, pp. 3151-3158, 1996).

The Examiner stated that Drebin et al. disclose hybridoma cell lines which secrete monoclonal antibodies that react specifically with cell-surface (i.e., extracellular) determinants found on NIH3T3 cells transfected with rat neuroblastoma DNA. The Examiner stated that the antibodies bind to and immunoprecipitate a phosphoprotein of relative molecular mass 185,000 (p185, the rat neu protein). The Examiner stated that Disis et al. are cited to show that the protein product of the rat neu gene is approximately 89% homologous to the human HER-2/neu protein (the Examiner notes that this reference is cited as evidence of the similarity of the rat and human proteins, not as prior art). The Examiner stated that in view of the similarity between the rat and human proteins, Drebin et al.'s antibodies are "capable of binding to p100 which is

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a human neu related protein...[which] corresponds substantially to the extracellular domain of the human neu gene product" and thus anticipate the instantly claimed hybridoma and monoclonal antibody.

In response, applicants respectfully traverse the rejection of claims 13 and 15 under 35 U.S.C. §102(b) as being anticipated by Drebin et al. in light of Disis et al. Applicants contend that Drebin et al. in light of Disis et al. do not anticipate the presently claimed invention.

First, applicants contend that Drebin et al. do not anticipate the claimed invention. Applicants are gathering data for submission in a Declaration Under 37 C.F.R. §1.132 which shows that the monoclonal antibody taught in Drebin et al., the 7.16.4 monoclonal antibody, does not react with human neu protein. Applicants will submit the Declaration to the United States Patent and Trademark Office shortly. Therefore, applicants contend that Drebin et al. do not anticipate the claimed invention since the monoclonal antibody disclosed by Drebin et al. is not capable of bindng to p100 which is a human neu related protein having a molecular weight in the range from about 97,000 to about 115,000 daltons wherein said protein corresponds substantially to the extracellular domain of the human neu gene product, said protein being detectable in a biological fluid.

Applicants maintain that Disis et al. is an improper reference under 35 U.S.C. §102(b). Applicants point out that all elements of the claimed invention must be anticipated by one reference under 35 U.S.C. §102(b). Applicants maintain that all elements of the claimed invention are not anticipated by Drebin et al. and that Disis et al. is cited in an attempt to teach one of the elements of the claimed invention not taught by Drebin et al. Furthermore, applicants maintain that the Disis et al. reference does not

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provide evidence of the similarity between rat and human neu proteins as stated by the Examiner. Without conceding that Disis et al. provides such evidence, applicants contend that if Disis et al. did provide such evidence, Drebin et al. in light of Disis et al. would not anticipate the claimed invention for the reasons stated hereinabove.

Disis et al. state in the abstract that "rat neu protein is 89% homologous to human HER-2/neu protein" to explain their use of a rat model. There is no data to support this contention in the Disis et al. paper. In fact, there is no full protein sequence comparison between human and rat neu proteins taught at all. Furthermore, applicants maintain that even if there were support for this statement in the Disis et al. reference, there would continue to be an 11% difference between the rat and human protein sequences as conceded by the Examiner. This sequence difference is not localized to a particular protein region in either Drebin et al. or in Disis et al. and thus could exist in the human p100 region. Therefore, Drebin et al. does not provide evidence of the similarity between rat and human neu protiens.

Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection under 35 U.S.C. §102(b).

**Rejection Under 35 U.S.C. §103 - McKenzie et al.**

The Examiner rejected claim 14 under 35 U.S.C. §103 as being unpatentable over McKenzie et al. (Oncogene, vol. 4, no. 5, pp. 543-548, May 1989).

The Examiner stated that McKenzie et al. disclose hybridoma cell lines secreting OD3 (HB 10204), NB-3 (HB 10205), and TA-1 (HB10206), all of which bind the extracellular domain of the human

neu gene product. The Examiner stated that the reference differs from the instant invention in not disclosing immunoreactive fragments of the monoclonal antibodies. However, the Examiner stated, it is conventional to prepare fragments of antibodies for use in diagnostic assays, and it would have been obvious for one of ordinary skill in the art to have prepared fragments of McKenzie et al.'s antibodies.

In response, applicants respectfully traverse the rejection of claim 14 under 35 U.S.C. §103 as being unpatentable over McKenzie et al. Applicants maintain that McKenzie et al. is not a proper reference under 35 U.S.C. §103 in view of the discussion hereinabove regarding support of the presently pending claims in U.S. Serial No. 07/182,501, filed April 18, 1988. Thus, applicants request that the Examiner reconsider and withdraw this ground of rejection.

**Rejection Under 35 U.S.C. §103 - Drebin et al. in light of Disis et al.**

The Examiner rejected claim 14 under 35 U.S.C. §103 as being unpatentable over Drebin et al. (Nature, vol 312, no. 5994, pp. 545-548, December 1984)(in light of Disis et al. (Journal of Immunology, vol. 156, no. 9, pp. 3151-3158, 1996)) as applied to claims 13 and 15 above.

The Examiner stated that Drebin et al. differ from the instant invention in not disclosing immunoreactive fragments of monoclonal antibodies capable of binding the extracellular domain of the human neu protein. The Examiner further stated that however, it is conventional to prepare fragments of antibodies for use in diagnostic assays, and the Examiner asserted that it would have been obvious for one of ordinary skill in the art to have prepared

fragments of Drebin et al.'s antibodies.

In response, applicants respectfully traverse the rejection of claim 14 under 35 U.S.C. §103 as being unpatentable over Drebin et al. (in light of Disis et al.). Applicants refer the Examiner to the discussion of Drebin et al. in light of Disis et al. hereinabove. Applicants maintain that Drebin et al. in light of Disis et al. do not render obvious the claimed invention of claim 14. Drebin et al. do not disclose or render obvious immunoreactive fragments of a monoclonal antibody which is capable of binding to p100 which is a human neu related protein having a molecular weight in the range from about 97,000 daltons to about 115,000 daltons wherein said protein corresponds substantially to the extracellular domain of the human neu gene product, said protein being detectable in a biological fluid. Drebin et al. do not suggest immunoreactive fragments of an antibody capable of binding to a protein, p100, which is a human neu related protein, of a molecular weight in a specific range. Drebin et al. do teach immunoreactive fragments of an antibody which binds to a protein of 185,000 molecular weight. This molecular weight is outside of the range recited in the claimed invention. Thus, applicants contend that Drebin et al. teaches away from the claimed invention. In addition, Drebin et al. does not teach antibodies to human neu related protein, but rather teach antibodies to rat proteins. Furthermore, Drebin et al. do not render obvious that the aforementioned p100 human neu related protein is detectable in a biological fluid. Applicants contend that Drebin et al. do not render obvious the claimed invention of claim 14.

Drebin et al. do not render obvious the presently claimed monoclonal antibodies and hybridoma cell lines. The specific monoclonal antibodies OD-3, NB3 and TA-1 would not be rendered obvious by the 7.16.4 antibody of Drebin et al. The Drebin et al.

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antibody is not capable of binding a human p100, nor is it the same isotype as each claimed antibody. Thus, Drebin et al. do not render obvious the claimed invention.

Applicants maintain that there is no motivation to combine Drebin et al. with Disis et al. The Drebin et al. reference teaches "monoclonal antibodies that identify a cell-surface antigen associated with an activiated cellular oncogene" while the Disis et al. reference teaches "peptide-based, but not whole protein, vaccines that elicit immunity to HER-2/neu, an oncogenic self-protein".

Applicants further maintain that Disis et al. do not remedy the shortcomings of the Drebin et al. reference. Disis et al. do not render obvious the claimed invention of immunoreactive fragments of the aforementioned monoclonal antibody of claim 14. Applicants point out that Disis et al. do not teach or render obvious p100, or a monoclonal antibody capable of binding to a protein in the molecular weight range recited hereinabove. Disis et al. do not render obvious that such p100 human neu related protein is detectable in a biological fluid.

In view of the above remarks, applicants contend that Drebin et al. in light of Disis et al. do not render obvious the claimed invention of claim 14. Applicants request that the Examiner reconsider and withdraw this ground of rejection.

**Rejection Under 35 U.S.C. §103 - Masuko et al.**

The Examiner rejected claims 14 and 16-18 under 35 U.S.C. §103 as being unpatentable over Masuko et al. (Jpn. J. Cancer Res., vol. 80, pp. 10-14, January 1989)

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The Examiner stated that Masuko et al. disclose a hybridoma cell line secreting a monoclonal antibody (SV2-61) which recognizes the extracellular domain of the human neu gene product (see the abstract).

The Examiner stated that with respect to claim 14, Masuko et al. differ from the instant invention in not disclosing immunoreactive fragments of monoclonal antibodies capable of binding the extracellular domain of the human neu protein. However, the Examiner stated, it is conventional to prepare fragments of antibodies for use in diagnostic assays, and it would have been obvious for one of ordinary skill in the art to have prepared fragments of Masuko et al.'s antibodies. The Examiner stated that with respect to claims 16-18 Masuko et al. differ from the instant invention in disclosing monoclonal antibodies OD3 (HB 10204), NB-3 (HB 10205), and TA-1 (HB 10206). However, the Examiner stated, SV2-61 recognizes the extracellular domain of the human neu gene product, and so has essentially the same binding properties as OD3, NB-3, and TA-1. The Examiner further stated that it would have been obvious for one of ordinary skill in the art to make other, patentably indistinguishable, antibodies to the extracellular domain.

In response, applicants respectfully traverse the rejection of claim 14 and 16-18 under 35 U.S.C. §103 as being unpatentable over Masuko et al. Applicants refer the Examiner to the discussion of hereinabove which points out that the presently claimed invention is supported in a related parent application U.S. Serial No. 07/182,501, filed April 18, 1988. Thus, applicants maintain that the Masuko et al. reference is an improper reference. Accordingly, applicants respecfully request the Examiner reconsider and withdraw this ground of rejection. Applicants solicit the allowance of pending claims 13-18.

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